

2.04.07 Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance

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Policy Statement

The use of urinary tumor markers is considered **investigational** in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

For the purpose of this policy, standard diagnostic procedures for bladder cancer consist of urine cytology and cystoscopy, with or without biopsy.

Coding

The BTA (bladder tumor antigen) *stat*[®] and nuclear matrix protein 22 (NMP22) are immunoassay tests.

When performed qualitatively in the physician's office, the following CPT codes may be used to describe the corresponding tests:

BTA *stat* Test

- **86294:** Immunoassay for tumor antigen, qualitative and semiquantitative (e.g., bladder tumor antigen)

NMP22 Test

- **86386:** Nuclear Matrix Protein 22 (NMP22), qualitative

For clinical laboratories performing a quantitative version of these tests, the following CPT code may be used to describe the test:

- **86316:** Immunoassay for tumor antigen; other antigen, quantitative (e.g., CA 50, 72-4, 549), each

There are specific CPT codes for urinary fluorescence in situ hybridization (FISH) testing:

- **88120:** Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
- **88121:** Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology

The CertNDx[™] test is likely to be reported with the following CPT code:

- **81479:** Unlisted molecular pathology procedure

The following CPT PLA code may be used for theascreen[®] Testing:

- **0154U:** Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (i.e., p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status

The following are specific MAA codes for Cxbladder:

- **0012M:** Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma

- **0013M:** Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma

The following is a code for the PolypDx test:

- **0002U:** Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps

Description

The diagnosis of bladder cancer is generally made by cystoscopy and biopsy. Bladder cancer has a very high frequency of recurrence and therefore follow-up cystoscopy, along with urine cytology, is done periodically to identify recurrence early. Urine biomarkers that might be used to supplement or supplant these tests have been actively investigated.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Table 1 lists urinary tumor marker tests approved or cleared for marketing by the FDA. The FDA approved or cleared tests are indicated as adjuncts to standard procedures for use in the initial diagnosis of bladder cancer or surveillance of bladder cancer patients.

Table 1. FDA Approved or Cleared Urinary Tumor Marker Tests

Test	Manufacturer	Type	Detection	Indication
BTA stat®	Polymedco	Point of care immunoassay	Human complement factor H-related protein	Qualitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer
BTA TRAK®	Polymedco	Reference laboratory immunoassay	Human complement factor H-related protein	Quantitative detection of bladder tumor-associated antigen in the urine of persons diagnosed with bladder cancer
Alere NMP22®	Alere	Immunoassay	NMP22 protein	in vitro quantitative determination of the nuclear mitotic apparatus protein (NuMA) in stabilized voided urine. Used as adjunct to cystoscopy
BladderChek®	Alere	Point of care immunoassay	NMP22 protein	Adjunct to cystoscopy in patients at risk for bladder cancer

Test	Manufacturer	Type	Detection	Indication
UroVysion®	Abbott Molecular	FISH ^a	Cell-based chromosomal abnormalities	Aid in the initial diagnosis of bladder cancer (P030052) and monitoring patients with previously diagnosed bladder cancer (K033982)

FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein.

^a FISH is a molecular cytogenetic technology that can be used with either DNA or RNA probes to detect chromosomal abnormalities. DNA FISH probe technology involves the creation of short sequences of fluorescently labeled, single-strand DNA probes that match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Urine-based tests are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests. Laboratory-developed tests include:

- Cxbladder Monitor (Pacific Edge) measures the expression of 5 genes (*MDK*, *HOXA13*, *CDC2*, *IGFBP5*, *CXCR2*). Pacific Edge also has Cxbladder Detect and Cxbladder Triage tests.
- Xpert® Bladder Cancer Monitor (Cepheid) measures mRNA (*ABL1*, *CRH*, *IGF2*, *UPK1B*, *ANXA10*) in voided urine by reverse transcription-polymerase chain reaction (RT-PCR).
- PolypDx™ (Metabolomic Technologies) is a urine metabolite assay that uses liquid chromatography-mass spectrometry. An algorithm compares urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.

Rationale

Background

Urinary Bladder Cancer

Urinary bladder cancer, a relatively common form of cancer in the U.S., results in significant morbidity and mortality. Bladder cancer (urothelial carcinoma) typically presents as a tumor confined to the superficial mucosa of the bladder. The most frequent symptom of early bladder cancer is hematuria; however, urinary tract symptoms (i.e., urinary frequency, urgency, dysuria) may also occur. Cigarette smoking is an important risk factor for urothelial carcinoma.

Diagnosis

The criterion standard for a confirmatory diagnosis of bladder cancer is cystoscopic examination with biopsy. At initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or subepithelial connective tissue. The non-muscle-invasive disease is usually treated with transurethral resection, with or without intravesical therapy, depending on the depth of invasion and tumor grade. However, a 50% to 75% incidence of recurrence has been noted in these patients, with 10% to 15% progressing to muscle invasion over a 5-year period. Current follow-up protocols include flexible cystoscopy and urine cytology every 3 months for 1 to 3 years, every 6 months for an additional 2 to 3 years, and then annually thereafter, assuming no recurrence.

While urine cytology is a specific test (from 90% to 100%), its sensitivity is lower, ranging from 50% to 60% overall, and it is considered even lower for low-grade tumors. Therefore, interest has been reported in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence.

Adjunctive testing to urine cytology has used a variety of nuclear and cytoplasmic targets, and a range of molecular pathology and traditional (e.g., immunohistochemistry) methods. Commercially available tests approved or cleared by the U.S. Food and Drug Administration (FDA) as well as laboratory-developed tests are summarized in the Regulatory Status section.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Urinary Tumor Marker Testing of Individuals with Symptoms of Bladder Cancer

Clinical Context and Test Purpose

The purpose of using urinary tumor markers in the evaluation of patients who have signs and/or symptoms of bladder cancer is to inform a decision whether to proceed to cytology and biopsy.

The question addressed in this evidence review is: Does the use of urinary tumor marker tests, in addition to routine cystoscopy, improve the net health outcome in individuals with signs and/or symptoms of bladder cancer?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with signs and/or symptoms of bladder cancer. This includes patients with no prior diagnosis who present with urinary symptoms suggestive of bladder cancer (most commonly unexplained microscopic hematuria).

Interventions

The test being considered is urinary tumor marker tests in addition to cystoscopy.

Comparators

The following practices are currently being used to assess individuals with signs and/or symptoms of bladder cancer: cystoscopy alone and cytology. Patients with microscopic hematuria with no etiology identified after an evaluation for glomerular disease or infection would typically be recommended for cystoscopy and biopsy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. Beneficial outcomes are primarily related to the detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

Although not completely standardized, follow-up for non-muscle-invasive bladder cancer would typically occur periodically over the course of years.

Study Selection Criteria

For the evaluation of the clinical validity of the urinary biomarkers for the indications within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Studies have evaluated the diagnostic performance of individual markers compared with urine cytology, the standard urine-based test for bladder tumor diagnosis and surveillance.

Cystoscopy and biopsy are generally used as the criterion standard comparison. Of particular interest are the relative performance of individual markers and the performance of individual markers compared with combinations of markers.

Several systematic reviews of diagnostic accuracy studies have been published. Chou et al (2015) reported on a systematic review and meta-analysis of studies of the diagnostic accuracy of urinary biomarkers for the diagnosis or follow-up of non-muscle-invasive bladder cancer, which was done as part of an Agency for Healthcare Research and Quality Comparative Effectiveness Review on the diagnosis and treatment of non-muscle-invasive bladder cancer.¹ Two studies were rated as having a low risk of bias, 3 studies at high risk of bias, and the remainder considered to have a moderate risk of bias. Only studies that used cystoscopy or histopathology as the reference standard were analyzed. Results of pooled analyses of diagnostic accuracy in patients with symptoms of bladder cancer are displayed in Table 2.

Table 2. Diagnostic Accuracy of Urinary Biomarkers in Patients With Symptoms of Bladder Cancer

Test	TP/n	Pooled Sensitivity (95% CI), %	Studies, n	Pooled Specificity (95% CI), %	Studies, n
BTA stat					
Quantitative test	37/49	76 (61 to 87)	1	53 (38 to 68)	1
Qualitative test	275/372	76 (67 to 83)	8	78 (66 to 87)	6
NMP22 BladderChek					
Quantitative test	235/368	67 (55 to 77)	9	84 (75 to 90)	7
Qualitative test	69/145	47 (33 to 61)	2	93 (81 to 97)	2
FISH (e.g., UroVysion)	82/144	73 (50 to 88)	2	95 (87 to 98)	1
Cxbladder	54/66	82 (70 to 90)	1	85 (81 to 88)	1

Adapted from Chou et al (2015).¹

CI: confidence interval; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein; TP: true positives.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No direct evidence was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of urinary biomarker testing has not been established, the conclusion of testing using these markers to diagnose individuals with signs and/or symptoms of bladder cancer cannot be drawn.

Section Summary: Urinary Tumor Marker Testing of Individuals With Symptoms of Bladder Cancer

Numerous studies have evaluated the accuracy of urinary tumor markers for diagnosing and/or monitoring bladder cancer. Systematic reviews of these studies have been published. In studies

on the initial diagnosis of bladder cancer, urinary tumor marker tests have pooled sensitivity ranging from 47% to 82% and pooled specificity ranging from 53% to 95% compared with cystoscopy and biopsy. There is no evidence of the clinical utility of urinary biomarker testing in this population.

Urinary Tumor Marker Testing for Individuals With a History of Bladder Cancer

Clinical Context and Test Purpose

The purpose of using urinary tumor markers in the evaluation of patients who have a history of bladder cancer is to monitor for recurrence and inform a decision whether to proceed to cytology and biopsy.

The question addressed in this evidence review is: Does the use of urinary tumor marker tests, in addition to routine cystoscopy, improve the net health outcome in individuals with a history of bladder cancer?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a history of bladder cancer.

Interventions

The test being considered is urinary tumor marker tests in addition to cystoscopy.

Comparators

The following practices are currently being used to assess individuals with a history of bladder cancer: cystoscopy alone and cytology.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test accuracy and validity, and resource utilization. Beneficial outcomes are primarily related to the detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

Although not completely standardized, follow-up for non-muscle-invasive bladder cancer would typically occur periodically over the course of years.

Study Selection Criteria

For the evaluation of the clinical validity of the urinary biomarkers for the indications within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews

Pooled analysis on the diagnostic accuracy of urinary biomarkers by Chou et al (2015) is provided in Table 3. The reference standard was cystoscopy or histopathology.

Table 3. Diagnostic Accuracy of Urinary Biomarkers in Patients With a History of Bladder Cancer

Test	TP/n	Pooled Sensitivity (95% CI), %	Studies, n	Pooled Specificity (95% CI), %	Studies, n
BTA stat					
Quantitative test	39/67	58 (46 to 69)	2	79 (72 to 85)	2
Qualitative test	325/544	60 (55 to 65)	11	76 (69 to 83)	8
NMP22 BladderChek					
Quantitative test	235/368	61 (49 to 71)	10	71 (60 to 81)	8
Qualitative test	99/159	70 (40 to 89)	2	83 (75 to 89)	2
FISH (e.g., UroVysion)	189/299	55 (36 to 72)	7	80 (66 to 89)	6

Adapted from Chou et al (2015).¹

CI: confidence interval; FISH: fluorescence in situ hybridization; NMP: nuclear matrix protein; TP: true positives.

Observational studies

The fibroblast growth factor receptor 3 (*FGFR3*) variants may be associated with lower grade bladder tumors that have a good prognosis. Several studies have evaluated urine-based assays for identifying *FGFR3* variants.

A study was published by Fernandez et al (2012); several coauthors were employees of Predictive Biosciences, the manufacturer of the CertNDx test.² The study included 323 individuals who had been treated for bladder cancer; 48 had recurrent bladder cancer and the remaining 275 had no current evidence of disease. Seven patients without disease did not have sufficient DNA for *FGFR3* variant testing and were excluded from further analysis. *FGFR3* variants were detected in 15 samples, 5 from patients with cancer recurrence and 10 from patients without evidence of disease. This resulted in a sensitivity of 5 (10%) of 48 and a specificity of 258 (96%) of 268.

Zuiverloon et al (2010) applied *FGFR3* variant analysis to the detection and prediction of bladder cancer recurrence.³ The research team, based in the Netherlands, developed an assay to identify common *FGFR3* variants in urine samples. This team identified tumor *FGFR3* variant status in 200 patients with low-grade non-muscle-invasive bladder cancer. *FGFR3* variants were identified in 134 (67%) patients. The sensitivity of the assay to detect concomitant recurrences was 26 (58%) of 45. After at least 12 months of follow-up from the last urine sample, an additional 34 recurrences were identified. Overall, 85 (81%) of 105 *FGFR3*-positive urine samples were associated with a bladder cancer recurrence compared with 41 (11%) of 358 *FGFR3*-negative urine samples. Using a Cox time-to-event analysis, an *FGFR3*-positive urine test was associated with a 3.8-fold higher risk of recurrence ($p < .001$).

Another study by Zuiverloon et al (2013) assessed a total of 716 urine samples collected from 136 patients with non-muscle-invasive bladder cancer (at least 3 samples per patient were required for study entry).⁴ During a median of 3 years of follow-up, there were 552 histologically proven bladder cancer recurrences. The sensitivity and specificity of *FGFR3* for detecting a recurrence were 201 (49%) of 408 and 124 (66%) of 187, respectively. In comparison, the sensitivity of cytology was 211 (56%) of 377 and the specificity was 106 (57%) of 185. Combining *FGFR3* and cytology increased sensitivity to 76% but lowered specificity to 42%.

Two studies prospectively evaluated the use of Xpert Bladder Cancer Monitor in a follow-up of patients with a history of non-muscle invasive bladder cancer. D'Elia et al (2021) followed 416 patients, of whom 168 patients had a new recurrence of non-muscle invasive bladder cancer. In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 52.4% and specificity of 78.4%; cytology demonstrated an overall sensitivity of 17.9% and specificity of 98.5%.⁵ Pichler et al (2018) followed 140 patients, of whom 43 patients had a new recurrence of non-muscle invasive bladder cancer. In these patients, Xpert Bladder Cancer Monitor demonstrated an overall sensitivity of 84% and specificity of 91%; cytology demonstrated an overall sensitivity of 33% and specificity of 94%. Blinding was not discussed for either study; studies were further limited by a short follow-up period.⁶

Clinically Valid

The diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 52% to 84% and pooled specificity ranging from 71% to 91%. There are several diagnostic performance studies on *FGFR3* for monitoring bladder cancer. These studies generally showed that the markers had higher sensitivity than cytology.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because of the potential consequences of missing a diagnosis of recurrent bladder cancer, it is unlikely that the standard timing of cystoscopies would be altered unless the sensitivity of urinary marker(s) approaches 100%. Some have suggested that consideration should be given to lengthening the intervals of cystoscopy in patients with low levels of an accurate marker and low-grade bladder cancer. In addition, while urinary tumor markers might not alter the schedule of cystoscopies, if their results suggest a high likelihood of tumor recurrence, the resulting cystoscopy might be performed more thoroughly, or investigation of the upper urinary tract might be initiated.⁷ No published studies were identified comparing different cystoscopy protocols, used in conjunction with urinary markers, to monitor recurrence.

Shariat et al (2011) used a decision curve analysis to assess the impact of urinary marker testing using the nuclear matrix protein 22 (NMP22) assay on the decision to refer for cystoscopy; the authors concluded that the marker did not aid clinical decision making in most cases.⁸ The study included 2222 patients with non-muscle-invasive bladder cancer and negative cytology, at various stages of surveillance. All patients underwent cystoscopy, and 581 (26%) were found to have disease recurrence. The NMP22 level was found to be significantly associated with both disease recurrence and progression ($p < .001$ for both). The investigators found only a small clinical net benefit for the NMP22 test over the strategy of "cystoscopy for all patients." For patients with at least a 15% risk of recurrence, using a model containing age, sex, and NMP22, 229 (23%) cystoscopies could be avoided, 236 (90%) recurrences would be identified, and 25 (15%) recurrences would be missed. Thus, for clinicians or patients who would opt for cystoscopy even if patients had a low-risk of recurrence (e.g., 5%), NMP22 would not add clinical benefit and the optimal strategy would be to offer cystoscopy to all at-risk patients.

Kim et al (2014) examined data on the fluorescence in situ hybridization (FISH) testing with the aim of determining whether the urinary marker could modify the surveillance schedule in patients with non-muscle-invasive bladder cancer who had suspicious cytology but a negative surveillance cystoscopy.⁹ The standard surveillance protocol at the study institution was providing cystoscopy and urinary cytology every 3 to 6 months. A total of 243 patients who met the previous criteria had FISH testing and a subgroup of 125 patients had subsequent surveillance cystoscopy 2 to 6 months after reflex FISH. The FISH results were not significantly associated with the results of the next cystoscopy (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.26 to 2.74; $p = 1.0$). Because of this lack of short-term association between FISH results and cystoscopy, the results suggest that FISH has limited ability to modify the surveillance schedule in non-muscle-invasive bladder cancer.

The purpose of the limitations tables (Tables 4 and 5) is to display notable limitations identified in each study.

Table 4. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Shariat et al (2011) ²	4. All patients had negative cytology		2. No control group	1. Management decisions	
Kim et al (2014) ²	4. All patients had negative cystoscopy		2. No control group		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Shariat et al (2011) ²	1.No allocation	1,2.No blinding				1. Decision curve analysis
Kim et al (2014) ²	1.No allocation	1,2.No blinding				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important differences.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Urinary Tumor Marker Testing for Individuals With a History of Bladder Cancer

Diagnostic accuracy studies report that urinary tumor marker tests have pooled sensitivity ranging from 55% to 75% and pooled specificity ranging from 71% to 83%. Direct evidence that outcomes are improved or not worsened with an altered schedule would be useful. However, no controlled studies were identified that prospectively evaluated health outcomes in patients managed with and without the use of urinary tumor marker tests. There is a lack of direct evidence that health outcomes improve in patients managed with urinary tumor marker tests compared with those managed without tumor marker tests. Furthermore, there is a lack of direct evidence that cystoscopy protocols would be changed when urinary tumor marker tests are used. The available studies have found a low potential clinical benefit of urinary tumor marker

testing for patients with non-muscle-invasive bladder cancer in terms of avoiding cystoscopy or lengthening intervals between cystoscopies.

Urinary Tumor Marker Tests To Screen Asymptomatic Individuals for Bladder Cancer

Clinical Context and Test Purpose

The purpose of screening tests with urinary markers in asymptomatic individuals at population-level risk is to detect bladder cancer at an earlier stage than it would present otherwise at a stage when treatment would permit improved outcomes.

The question addressed in this evidence review is: Does population-level screening with urinary tumor marker tests improve the net health outcome in asymptomatic individuals?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic and at a population-level risk of bladder cancer.

Interventions

The test being considered is urinary tumor marker tests.

Comparators

The following practices are currently being used to assess asymptomatic individuals at population-level risk of bladder cancer: standard surveillance without urinary tumor marker testing. At present, there is no standard population-level screening for bladder cancer. Patients typically present with signs and/or symptoms, such as hematuria.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test accuracy, and test validity. Beneficial outcomes are primarily related to the detection of disease that would have been missed without the test. Harmful outcomes are related to unneeded invasive testing due to false-positive testing.

If indicated, screening for non-muscle-invasive bladder cancer would typically occur periodically over the course of years.

Study Selection Criteria

For the evaluation of the clinical validity of the urinary biomarkers for the indications within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Review

The ideal study for evaluating the effectiveness of a screening program is an RCT comparing outcomes in patients who did and did not participate in a screening program. Chou et al (2010) updated a U.S. Preventive Services Task Force evidence review on screening adults for bladder cancer.¹⁰ The quality of evidence was rated low that screening for bladder cancer reduces morbidity or mortality. There were no RCTs, and only 1 prospective study rated as poor quality. The systematic review did not identify any studies evaluating the sensitivity or specificity of

diagnostic tests for bladder patients in asymptomatic average-risk patients. Moreover, reviewers did not identify any suitable studies assessing whether the treatment of screen-detected bladder cancer reduces disease-specific morbidity and mortality or evaluating potential harms of screening for bladder cancer. Reviewers concluded: "major gaps in evidence make it impossible to reach any reliable conclusions about screening."

Observational Studies

Several uncontrolled studies have reported on screening studies. Bangma et al (2013) reported on a population-based program with men in the Netherlands.¹¹ The study evaluated the feasibility of screening using urine-based markers and examined performance characteristics of screening tests. The screening protocol consisted of 14 days of home urine testing for hematuria. Men with at least 1 positive home hematuria test underwent screening for 4 urine-based molecular markers. Men with at least 1 positive urine-based test were recommended to undergo cystoscopy. Of 6500 men invited to participate in screening, 1984 (30.5%) agreed and 1747 (88.1%) underwent hematuria testing. Of these, 409 (23.4%) tested positive for hematuria and 385 (94%) underwent urine-based marker testing. Cancer was diagnosed in 4 (0.002%) of 1747 men who underwent screening (3 bladder cancers, 1 kidney cancer). Although men in the study who tested negative on screening tests did not receive further testing, the investigators were able to link participants' data to a Dutch cancer registry. The investigators determined that 2 cancers (1 bladder cancer, 1 kidney cancer) had been diagnosed in men who completed the protocol; these were considered false-negatives. The sensitivity and specificity of the U.S. Food and Drug Administration approved NMP22 test were 25% (95% CI, 0.63% to 80.6%) and 96.6% (95% CI, 94.2% to 98.2%), respectively. The screening program had a low diagnostic yield.

Lotan et al (2009) published a prospective study that screened 1502 individuals at high-risk of bladder cancer due to age plus smoking and/or occupational exposure.¹² Individuals with positive BladderChek tests received cystoscopy and cytology. Eighty-five (5.7%) of the 1502 participants had a positive BladderChek test. Two of the 85 patients were found to have bladder cancer (noninvasive), yielding a positive predictive value of 2.4%. There was also 1 case of atypia. Follow-up at a mean of 12 months was obtained for 1309 (87%) of 1502 screened patients. No additional cancers were diagnosed in the group that had positive BladderChek tests. Two participants with a negative BladderChek screen had been diagnosed with bladder cancer; both tumors were less than 1 cm. Because no follow-up tests were done on participants who initially tested negative, it is unclear whether these were false-negative findings or new cancers. Study limitations included lack of follow-up testing on approximately 20% of participants who tested positive and lack of early cystoscopy and incomplete 1-year telephone follow-up in those who tested negative. Because of these limitations, accurate test operating characteristics (e.g., sensitivity) cannot be calculated.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No evidence was identified addressing the impact of screening using urinary biomarker testing to diagnose bladder cancer.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of screening using urinary biomarkers in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Urinary Marker Tests to Screen Asymptomatic Individuals for Bladder Cancer

We found no RCTs evaluating the impact of screening for cancer on health outcomes in asymptomatic individuals. There is also insufficient observational evidence on the diagnostic accuracy of urinary tumor markers used to screen asymptomatic individuals for bladder cancer.

Urinary Marker Tests to Screen Asymptomatic Individuals for Precancerous Colonic Polyps Clinical Context and Test Purpose

The purpose of screening tests for urinary markers in asymptomatic individuals is to detect disease at an earlier stage than it would present otherwise when treatment would permit improved outcomes. Screening for polyps is currently conducted by colonoscopy, with a U.S. Preventive Services Task Force recommendation of screening every 10 years beginning at 45 years of age.¹³ Colonoscopy is invasive and uncomfortable and results in poor compliance with screening recommendations. The availability of a noninvasive test for precancerous polyps could improve referral for colonoscopy and early detection of colon cancer.

The question addressed in this evidence review is: Does population-level screening for precancerous colonic polyps using urinary markers improve the net health outcome in asymptomatic individuals?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic and at a population-level risk of colon cancer.

Interventions

The test being considered is urinary tests for precancerous polyps (PolypDx). PolypDx is a urine metabolite assay that uses an algorithm to compare urine metabolite concentrations to determine the likelihood of colonic adenomatous polyps.

Comparators

The following practices are currently being used to assess asymptomatic individuals at population-level risk of colon cancer: colonoscopy and fecal testing. The U.S. Preventive Services Task Force has recommended screening for colon cancer starting at age 45 and continuing until age 75.¹³ The criterion standard for screening for adenomatous polyps is a colonoscopy. Alternative methods for screening include computed tomography colonography and fecal tests.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test accuracy, and test validity. Beneficial outcomes are primarily related to the detection of disease that would have been missed without the test. Harmful outcomes are related to unnecessary invasive testing due to a false-positive result.

Follow-up for precancerous polyps would typically occur periodically over the course of years.

Study Selection Criteria

For the evaluation of the clinical validity of the urinary biomarkers for the indications within this review, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Validation Study

Deng et al (2017) reported on the development and validation of PolypDx. Urine and stool samples were prospectively collected from 695 individuals participating in a colorectal cancer screening program to undergo colonoscopy.¹⁴ Metabolites in urine that were associated with adenomatous polyps were determined from 67% of the samples using nuclear magnetic resonance spectroscopy. Blinded testing on the validation set was performed in 33% of the samples using mass spectrometry, with a resulting area under the curve of 0.692.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No direct evidence on clinical utility was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of screening using urinary biomarkers in this population has not been established, a chain of evidence supporting clinical utility cannot be constructed.

Section Summary: Urinary Marker Tests to Screen Asymptomatic Individuals for Precancerous Colon Polyps

The clinical data supporting a urine metabolite assay for adenomatous polyps involves a report of a training and validation set. There is insufficient evidence on the diagnostic accuracy of urinary tumor markers to draw conclusions about its use to screen asymptomatic individuals for precancerous colon polyps.

Summary of Evidence

For individuals who have signs and/or symptoms of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have a sensitivity ranging from 47% to 82% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a history of bladder cancer who receive urinary tumor marker tests in addition to cystoscopy, the evidence includes a number of diagnostic accuracy studies and meta-analyses, as well as a decision curve analysis and a retrospective study examining the clinical utility of urinary tumor marker tests. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. The diagnostic accuracy studies found that urinary tumor marker tests have pooled sensitivity ranging from 52% to 84% and pooled

specificity ranging from 71% to 91%. The decision analysis found only a small clinical benefit for use of a urinary tumor marker test and the retrospective study found that a urinary tumor marker test was not significantly associated with findings of the subsequent surveillance cystoscopy. No studies using the preferred trial design to evaluate clinical utility were identified; i.e., controlled studies prospectively evaluating health outcomes in patients managed with and without the use of urinary tests or prospective studies comparing different cystoscopy protocols used in conjunction with urinary tumor markers. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at a population-level risk of bladder cancer who receive urinary tumor marker tests, the evidence includes a systematic review and several uncontrolled prospective and retrospective studies. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A 2010 systematic review (conducted for the U.S. Preventive Services Task Force) did not identify any RCTs, the preferred trial design to evaluate the impact of population-based screening and found only 1 prospective study that the Task Force rated as poor quality. A more recent retrospective study, assessing a population-based screening program in the Netherlands, reported low diagnostic yield. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at a population-level risk of colon cancer who receive urinary tests for precancerous polyps, the evidence includes a validation study. Relevant outcomes are OS, disease-specific survival, and test accuracy and validity. The clinical data supporting a urine metabolite assay for adenomatous polyps includes a report of a training and validation set published in 2017. Current evidence does not support the diagnostic accuracy of urinary tumor markers to screen asymptomatic individuals for precancerous polyps. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received through 2 physician specialty societies and 5 academic medical centers in 2012. There was a unanimous agreement that urinary tumor markers approved by the U.S. Food and Drug Administration may be considered medically necessary as an adjunctive test in the diagnosis and monitoring of bladder cancer in conjunction with standard diagnostic procedures. In contrast, there was mixed support, but no consensus on the incremental value of urinary tumor markers compared with urinary cytology alone and for whether urinary tumor markers lead to changes in patient management. There was a unanimous agreement that the use of urinary tumor markers is investigational to screen for bladder cancer in asymptomatic subjects.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v. 5.2021) bladder cancer guidelines include consideration for urinary urothelial tumor markers every 3 months along with urine cytology for the first 2 years of follow-up for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation).¹⁵ The guidelines include the following statement: "Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumors may be considered during surveillance of high-risk non-muscle-invasive bladder cancer. However, it remains unclear whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors."

American Urological Association and Society of Urologic Oncology

The guidelines from the American Urological Association and Society of Urologic Oncology (2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review completed by the Agency for Health Care Research and Quality and through additional supplementation that further addressed key questions and more recently published literature.¹⁶ Table 6 summarizes statements on the use of urine markers after the diagnosis of bladder cancer.

Table 6. Guidelines for Urine Tumor Markers After the Diagnosis of Bladder Cancer

Guidance Statement	SOR	LOE
"In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation."	Strong	B
"In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance."		Expert opinion
"In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™)."		Expert opinion

BCG: bacillus Calmette-Guérin; FISH: fluorescence in situ hybridization; LOE: level of evidence; NMIBC: non-muscle-invasive bladder cancer; SOR: strength of recommendation.

American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction

In 2020, the American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a guideline on the diagnosis, evaluation, and follow-up of microhematuria.¹⁷ This guideline recommended the following with regard to urinary markers:

- Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria. [Strong recommendation; Evidence level: Grade C]
- Clinicians may obtain urine cytology for patients with persistent microhematuria after a negative workup who have irritative voiding symptoms or risk factors for carcinoma in situ. [Expert opinion]

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2011) concluded that there was insufficient evidence to assess the benefits and harms of screening for bladder cancer in asymptomatic adults.¹⁸ The recommendation was based on insufficient evidence (grade I). In April 2019, a literature surveillance report was published that scanned for relevant literature in PubMed and PubMed databases and the Cochrane library from 2009 to present.¹⁹ The researchers found "no relevant systematic reviews on the impact of screening for bladder cancer on morbidity and mortality, outcomes of treatment of screen-detected bladder cancer, or harms of screening for or treatment of screen-detected bladder cancer." Additionally, "no randomized, controlled trials or controlled observational studies compared the benefits or harms of treatment of screen-detected bladder cancer with no treatment."

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04100733	Surveillance of High-grade Non-muscle Invasive Bladder Tumors Using the Expert Bladder Cancer Monitor	392	Sep 2029
NCT03973307	Evaluation of UroX™ Biomarker Screening Test in the Investigation of Bladder Cancer From Urine Samples - a Single Site Pilot Study	100	Jul 2025
NCT05080998	An Observational Study of Cxbladder Monitoring for Recurrence of Urothelial Carcinoma in Intermediate and High-Risk Patients	450	Dec 2025
NCT03664258^a	Evaluation of the Xpert® Bladder Cancer Monitor Assay Compared to Cystoscopy for the Follow-up of Patients With History of Low or Intermediate Risk Non-muscle-invasive Bladder Cancer (NMIBC): an Observational Prospective Interventional Multicenter Study	852	Sep 2022
Unpublished			
NCT03125460^a	Clinical Evaluation of Xpert Bladder Cancer Monitor for Monitoring the Recurrence of Bladder Cancer	424	May 2019 (Completed)
NCT02969109^a	Clinical Validation of a Urine-based Assay With Genomic and Epigenomic Markers for Predicting Recurrence During Surveillance for Non-muscle Invasive Bladder Cancer	380	Sep 2018 (Completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

References

1. Chou R, Buckley D, Fu R, et al. Emerging Approaches to Diagnosis and Treatment of NonMuscle-Invasive Bladder Cancer (Comparative Effectiveness Review No. 153). Rockville, MD: Agency for Healthcare Research and Quality; 2015
2. Fernandez CA, Millholland JM, Zwarthoff EC, et al. A noninvasive multi-analyte diagnostic assay: combining protein and DNA markers to stratify bladder cancer patients. *Res Rep Urol.* 2012; 4: 17-26. PMID 24199176
3. Zuiverloon TC, van der Aa MN, van der Kwast TH, et al. Fibroblast growth factor receptor 3 mutation analysis on voided urine for surveillance of patients with low-grade non-muscle-invasive bladder cancer. *Clin Cancer Res.* Jun 01 2010; 16(11): 3011-8. PMID 20404005
4. Zuiverloon TC, Beukers W, van der Keur KA, et al. Combinations of urinary biomarkers for surveillance of patients with incident nonmuscle invasive bladder cancer: the European FP7 UROMOL project. *J Urol.* May 2013; 189(5): 1945-51. PMID 23201384
5. D'Elia C, Folchini DM, Mian C, et al. Diagnostic value of Xpert (R) Bladder Cancer Monitor in the follow-up of patients affected by non-muscle invasive bladder cancer: an update. *Ther Adv Urol.* Jan-Dec 2021; 13: 1756287221997183. PMID 33747133
6. Pichler R, Fritz J, Tulchiner G, et al. Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance. *BJU Int.* Jan 2018; 121(1): 29-37. PMID 28941000
7. Grocela JA, McDougal WS. Utility of nuclear matrix protein (NMP22) in the detection of recurrent bladder cancer. *Urol Clin North Am.* Feb 2000; 27(1): 47-51, viii. PMID 10696244
8. Shariat SF, Savage C, Chromecki TF, et al. Assessing the clinical benefit of nuclear matrix protein 22 in the surveillance of patients with nonmuscle-invasive bladder cancer and

- negative cytology: a decision-curve analysis. *Cancer*. Jul 01 2011; 117(13): 2892-7. PMID 21692050
9. Kim PH, Sukhu R, Cordon BH, et al. Reflex fluorescence in situ hybridization assay for suspicious urinary cytology in patients with bladder cancer with negative surveillance cystoscopy. *BJU Int*. Sep 2014; 114(3): 354-9. PMID 24128299
 10. Chou R, Dana T. Screening adults for bladder cancer: a review of the evidence for the U.S. preventive services task force. *Ann Intern Med*. Oct 05 2010; 153(7): 461-8. PMID 20921545
 11. Bangma CH, Loeb S, Busstra M, et al. Outcomes of a bladder cancer screening program using home hematuria testing and molecular markers. *Eur Urol*. Jul 2013; 64(1): 41-7. PMID 23478169
 12. Lotan Y, Elias K, Svatek RS, et al. Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. *J Urol*. Jul 2009; 182(1): 52-7; discussion 58. PMID 19450825
 13. US Preventative Services Task Force. Colorectal cancer screening. 2021; <https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/colorectal-cancer-screening>. Accessed October 26, 2021
 14. Deng L, Chang D, Foshaug RR, et al. Development and Validation of a High-Throughput Mass Spectrometry Based Urine Metabolomic Test for the Detection of Colonic Adenomatous Polyps. *Metabolites*. Jun 22 2017; 7(3). PMID 28640228
 15. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 5.2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed October 25, 2021
 16. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol*. Oct 2016; 196(4): 1021-9. PMID 27317986
 17. Barocas DA, Boorjian SA, Alvarez RD, et al. Microhematuria: AUA/SUFU Guideline. *J Urol*. Oct 2020; 204(4): 778-786. PMID 32698717
 18. U.S. Preventive Services Task Force (USPSTF). Bladder cancer in adults: Screening. Recommendation statement. 2011; <https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/bladder-cancer-in-adults-screening>. Accessed October 24, 2021
 19. U.S. Preventive Services Task Force Literature Surveillance Report Bladder Cancer in Adults: Screening. 2019. <https://www.uspreventiveservicestaskforce.org/uspstf/document/literature-surveillance-report/bladder-cancer-in-adults-screening>. Accessed October 23, 2021.
 20. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.07 (December 2021).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0002U	Oncology (colorectal), quantitative assessment of three urine metabolites (ascorbic acid, succinic acid and carnitine) by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring acquisition, algorithm reported as likelihood of adenomatous polyps
	0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
	0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
	0154U	Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (i.e., p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status
	81479	Unlisted molecular pathology procedure
	86294	Immunoassay for tumor antigen, qualitative or semiquantitative (e.g., bladder tumor antigen)
	86316	Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each
	86386	Nuclear Matrix Protein 22 (NMP22), qualitative
	88120	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121	Cytopathology, in situ hybridization (e.g., FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology	
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/07/2006	Policy Adopted - BCBSA MPP
01/07/2011	Policy title change from Urinary Tumor Markers for Bladder Cancer Policy revision with position change
01/21/2011	Coding Update
03/13/2012	Coding Update
10/05/2012	Policy revision with position change
12/14/2012	Policy revision with position change
06/30/2015	Policy title change from Urinary Tumor Markers Policy revision without position change
02/01/2017	Coding update
03/01/2017	Policy revision without position change
08/01/2017	Policy revision without position change
09/01/2018	Policy title change from Urinary Tumor Markers for Bladder Cancer

Effective Date	Action
	Policy revision without position change
03/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated Coding update
07/01/2020	Coding update
02/01/2021	Annual review. No change to policy statement. Literature review updated.
02/01/2022	Annual review. No change to policy statement. Policy guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance 2.04.07</p> <p>Policy Statement: The use of urinary tumor markers is considered investigational in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.</p>	<p>Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance 2.04.07</p> <p>Policy Statement: The use of urinary tumor markers is considered investigational in the screening, diagnosis of, and monitoring for bladder cancer, or screening for precancerous colonic polyps.</p>